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1-[2-[(Heteroaryloxy)heteroaryl]carbamoyl]indolines: Novel and Selective 5-HT_{2C} Receptor Inverse Agonists with Potential as Antidepressant/Anxiolytic Agents

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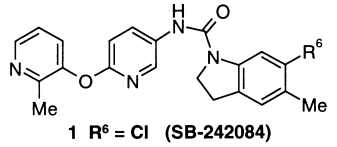
Abstract—Bisaryl ethers have been identified with excellent 5-HT_{2C} affinity and selectivity over both 5-HT_{2A} and 5-HT_{2B} receptors. Compounds such as **11**, **27** and **38** have potent oral activity in a centrally mediated pharmacodynamic model of 5-HT_{2C} function and their potential as novel non-sedating anxiolytic and antidepressants is under investigation.

The 5-HT_2 receptor family consists of 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes which were grouped together on the basis of their primary structure, secondary messenger system and pharmacological profile.[1] The last few years have seen extensive interest in the development of selective 5-HT_{2C} ligands as potential treatments for a range of CNS disorders, in particular anxiety and depression.[2,3] We have recently disclosed a number of bispyridyl ethers, such as **1** (SB-242084)[4] and **2** (SB-243213) which are potent 5-HT_{2C} receptor inverse agonists with selectivity over both the 5-HT_{2A} and 5-HT_{2B} receptors and potent in vivo activity in a number of animal models of anxiety.[3,5] Compound **2** is currently in phase 1 clinical trials for the treatment of depression and anxiety.[3] We now describe a detailed SAR around these compounds which has led to the identification of further high affinity and selective 5-HT_{2C} receptor inverse agonists with potent oral activity in a number of animal models.



1 R^6 = Cl (SB-242084)

2 R^6 = CF_3 (SB-243213)

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Chemistry

The final compounds were prepared according to Schemes 1–3. **1**–**37** were obtained by treating the anion of the appropriately substituted 3-hydroxypyridines or 4-methyl-5-hydroxypyrimidine[6] (in the case of **33**) with appropriately substituted 2-chloro-5-nitropyridines to afford the nitrobisaryl ethers in generally excellent yield (Scheme 1). Reduction to the corresponding amines and coupling with the appropriate substituted indolines,[7] via the phenyl carbamate, afforded the final compounds.[4] The 3-hydroxypyridines and 2-chloro-5-nitropyridines were all commercially available or known in the literature. The pyrimidine **40** was similarly prepared starting from 2-chloro-5-nitropyrimidine[8] and 3-hydroxy-2-methylpyridine. The pyridazines **38** and **39** were prepared by an analogous route (Scheme 2) by treating 3-amino-6-chloropyridazine with 3-hydroxy-2-methylpyridine and aqueous sodium hydroxide at high temperature to afford the amino bisarylether which was then coupled with the appropriate indoline as above. The pyrazine **41** was prepared by reacting 5-chloropyrazinecarboxylic acid methyl ester[9] with 3-hydroxy-2-methylpyridine under basic conditions to give the bisaryl ether (Scheme 3). The ester was then converted to the azide which was heated to generate the isocyanate and reacted in situ with 5-methyl-6-trifluoromethylindoline to afford **41**.

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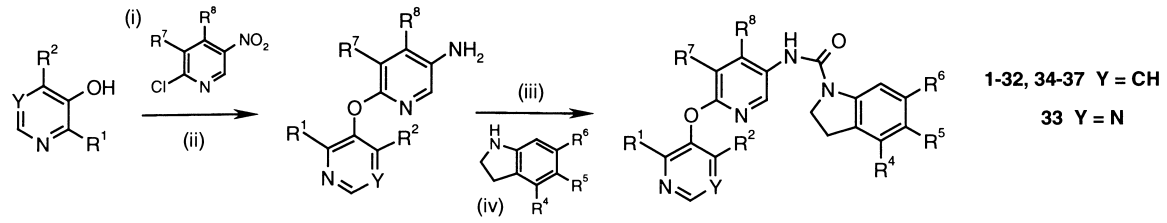
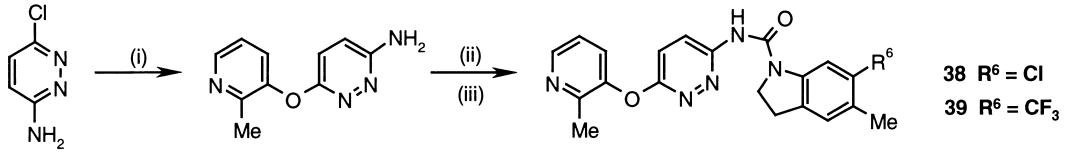
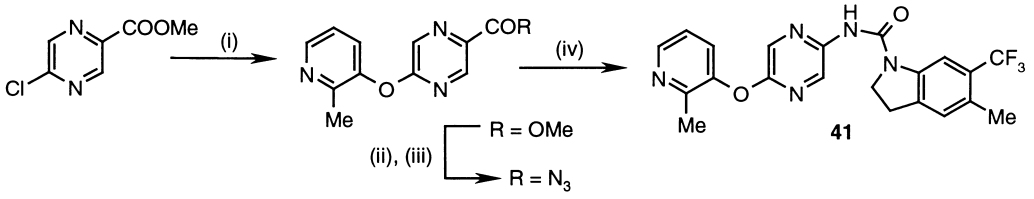


Scheme 1. Reagents and conditions: (i) NaH, DMF, 0 °C–rt, 18 h (25–95%); (ii) $SnCl_2$, EtOH/concd HCl, 50 °C, 1 h (80–100%); (iii) PhOCOCl/NEt_3,CH_2Cl_2, −20 °C, 1 h; (iv) NEt_3/DMF, 100 °C, 1 h (35–85%).



Scheme 2. Reagents and conditions: (i) 3-hydroxy-2-methylpyridine, NaOH, H_2O, 175 °C, bomb, 24 h (14%); (ii) PhOCOCl/NEt_3, CH_2Cl_2, −20 °C, 1 h; (iii) 5-methyl-6-R^6-indoline, NEt_3/DMF, 100 °C, 1 h (65%).



Scheme 3. Reagents and conditions: (i) 3-hydroxy-2-methylpyridine/NaH, DMF, 0 °C–rt, 1 h (94%); (ii) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, 4 h (76%); (iii) $NaNO_2$, aqueous HCl, 0 °C, 0.5 h (74%); (iv) 5-methyl-6-trifluoromethylindoline, toluene, reflux, 1 h (63%).

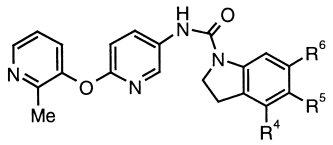
Optimization of indoline substitution (Table 1)

In marked contrast to a previous series of 1-(3-pyridylcarbamoyl)indolines,[4] where 5,6-disubstitution of the indoline was crucial for selectivity and 4-substitution detrimental, the bispyridyl ethers **1**–**26** retained selectivity over both 5-HT_{2A} and 5-HT_{2B} with a variety of indoline substitution. Surprisingly, even the unsubstituted indoline **3**, despite having a pK_i of only 7.0 at the 5-HT_{2C} receptor retained ~100-fold selectivity over 5-HT_{2A} affinity. The 4-CF_3 analogue **6** demonstrated a similar profile to **3**, whereas the 4-halo analogues **4** and **5** showed increased affinity and selectivity. The 5-monosubstituted indolines **7**–**11** demonstrated even greater 5-HT_{2C} affinity and the most impressive selectivities. The 6-monosubstituted indolines **12** and **13** had similar 5-HT_{2C} affinity but somewhat reduced selectivity over 5-HT_{2A}. Despite excellent in vitro profiles, from the monosubstituted analogues only **11** showed significant in vivo activity in the rat hypolocomotion model (ID_{50} of 2.1 mg/kg po). In this centrally mediated pharmacodynamic model of 5-HT_{2C} function, the ability of compounds to block the hypolocomotion in rats produced by a standard dose of the moderately selective 5-HT_{2C} agonist *m*-chlorophenylpiperazine (mCPP) was measured.[5] Disubstitution was found to have a beneficial additive effect on 5-HT_{2C} affinity with both 4,5- and 5,6-disubstitution affording excellent affinity and selectivity (**1**, **2** and **14**–**24**). The 4,5-disubstituted analogues **14** and **15** had greatest selectivity but unfortunately were inactive in vivo. In contrast some of the 5,6-disubstituted compounds such as **1**, **2** and **23** showed potent oral activity in the hypolocomotion model. The trisubstituted analogues **25** and **26** also demonstrated nanomolar 5-HT_{2C} affinity and modest oral activity but reduced selectivity. From this study **1** and **2** emerged as the compounds with best overall profiles combined with favourable metabolic stability. Therefore, either 5-chloro- or 5-trifluoro-6-methylindoline was incorporated into subsequent compounds prepared to further investigate modifications to other parts of the molecule.

Optimization of terminal aryl ring (Table 2)

We have previously reported that the 2-methyl group of the terminal pyridyl ring is important for selectivity.[4] Therefore, further modifications series were restricted to the 2- and 4-positions. Increasing the size of the 2-substituent from methyl to ethyl gave **27** with a similar profile to **1** but reduced selectivity over 5-HT_{2B}. The ^{n}Pr analogue **28** showed a similar binding profile but poor in vivo activity. The ^{i}Pr analogue **29** suffered a dramatic fall in 5-HT_{2C} affinity. The 2-Cl analogue **30** exhibited twofold reduced 5-$HT_{2A/B}$ selectivity and oral activity relative to **1**. The 4-methyl **31** and 4-chloro **32** analogues maintained excellent 5-HT_{2C} affinity but lacked selectivity as did the pyrimidine **33**. These findings confirm the 2-methyl-3-pyridyl ring as optimal in this series.

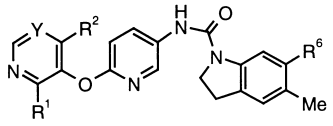
Table 1. The 5-$HT_{2A/B/C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of substituted 1-[2-[[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]indolines **1**–**26**



Compound	R^4	R^5	R^6	pK_i	pK_i (selectivity)		ID_{50}[e] (mg/kg po)
				5-HT_{2C}[b]	5-HT_{2A}[c]	5-HT_{2B}[d]	
3	H	H	H	7.0	< 5.0 (>100)	5.7 (20)	—
4	Cl	H	H	7.8	< 5.0 (>630)	5.6 (160)	6%
5	Br	H	H	7.8	< 5.2 (>400)	5.7 (>130)	3%
6	CF_3	H	H	6.7	< 5.0 (>50)	< 5.0 (>50)	—
7	H	F	H	7.4	< 5.0 (>250)	5.3 (130)	4%
8	H	Cl	H	8.2	< 5.0 (>1600)	5.7 (320)	40%
9	H	Br	H	8.5	< 5.4 (>1300)	6.2 (200)	10%
10	H	I	H	8.5	5.8 (500)	6.5 (100)	14%
11	H	CF_3	H	8.4	5.6 (630)	6.2 (160)	2.1
12	H	H	Cl	8.4	6.5 (80)	6.1 (200)	3%
13	H	H	CF_3	8.3	6.8 (30)	6.4 (80)	—
14	Br	Me	H	8.8	< 6.0 (>630)	6.6 (160)	0%
15	Cl	Cl	H	8.5	5.5 (1000)	6.3 (160)	4%
16	H	F	Cl	8.2	6.3 (80)	6.2 (100)	16%
17	H	Cl	Cl	8.7	6.6 (130)	6.5 (160)	32%
18	H	Br	CF_3	8.9	6.9 (100)	7.0 (80)	2%
19	H	Me	F	8.8	6.1 (500)	6.8 (100)	46%
1	H	Me	Cl	9.0	6.8 (160)	7.0 (100)	2.0
20	H	Me	Br	9.1	6.8 (200)	7.2 (80)	49%
2	H	Me	CF_3	9.0	6.8 (160)	7.0 (100)	1.0
21	H	Et	CF_3	8.6	6.3 (200)	6.9 (50)	12%
22	H	Cl	Me	8.9	6.8 (130)	6.9 (100)	7.3
23	H	OMe	CF_3	9.2	6.1 (1300)	7.3 (80)	2.8
24	H	SMe	CF_3	9.4	6.6 (630)	7.4 (100)	31%
25	Cl	Me	Cl	9.0	7.2 (60)	7.4 (40)	85%
26	CH_2CH_2O–		CF_3	8.9	6.3 (400)	7.2 (50)	9.0

[a]All values represent the mean of at least two determinations, with each determination lying within 0.2 log unit of the mean.
[b]Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]-mesulergine).[4]
[c]Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]-ketanserin).[4]
[d]Binding affinity (human cloned receptors; HEK 293 cells; [^{3}H]-5-HT).[4]
[e]Dose of compound required to reverse mCPP (7 mg/kg i.p. admin 30 min pretest) induced hypolocomotion by 50% or percentage reversal at 5 mg/kg.[4]

Table 2. The 5-$HT_{2A/B/C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of 1-[2-[2-(aryloxy)-5-pyridyl]carbamoyl]indolines **1**, **27**–**33**



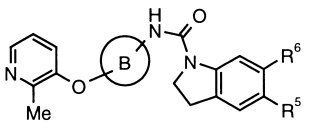
Compound	Y	R^1	R^2	R^6	pK_i	pK_i (selectivity)		ID_{50}[e] (mg/kg po)
					5-HT_{2C}[b]	5-HT_{2A}[c]	5-HT_{2B}[d]	
1	CH	Me	H	Cl	9.0	6.8 (160)	7.0 (100)	2.0
27	CH	Et	H	Cl	8.7	6.7 (100)	7.3 (25)	1.8
28	CH	^{n}Pr	H	Cl	8.8	6.8 (100)	7.0 (60)	18%
29	CH	^{i}Pr	H	Cl	6.9	6.1 (6)	6.7 (2)	—
30	CH	Cl	H	Cl	8.9	7.0 (80)	7.3 (40)	4.5
31	CH	H	Me	Cl	9.0	8.1 (8)	7.5 (30)	—
32	CH	H	Cl	Cl	9.3	7.8 (30)	7.9 (25)	—
33	N	Me	H	CF_3	8.7	7.1 (40)	7.9 (6)	—

[a–e]See corresponding footnotes in Table 1.

Optimization of central aryl ring (Table 3)

Introduction of a methyl group into the 4-position (**34**) was clearly not tolerated as had previously been observed in the simple biaryl series. Although the 3-methylpyridyl **35** had high 5-HT_{2C} affinity combined with good oral activity, the compound failed to achieve 100-fold selectivity over 5-HT_{2A} receptors. The 3-chloro

Table 3. The 5-$HT_{2A/B/C}$ receptor binding affinities,[a] selectivities over 5-HT_{2A} and 5-HT_{2B} and in vivo activity[e] of 1-[[2-[(2-methyl-3-pyridyl) oxy]aryl]carbamoyl]indolines **1** and **34–41**



Compound	B	R^5	R^6	pK_i	pK_i (selectivity)		ID_{50}[e] (mg/kg po)
				5-HT_{2C}[b]	5-HT_{2A}[c]	5-HT_{2B}[d]	
1		Me	Cl	9.0	6.8 (160)	7.0 (100)	2.0
34		OMe	CF_3	6.7	6.2 (3)	6.6 (1.3)	—
35		Me	Cl	8.8	6.9 (80)	7.5 (20)	0.8
36		Me	CF_3	8.8	6.6 (160)	7.4 (25)	>5
37		Me	Cl	9.2	6.9 (200)	7.7 (30)	>5
38		Me	Cl	8.7	5.8 (800)	6.8 (80)	1.6
39		Me	CF_3	8.5	6.4 (130)	6.9 (40)	1.2
40		Me	Cl	8.5	< 6.2 (>200)	7.2 (20)	3.7
41		Me	CF_3	8.7	6.2 (320)	7.1 (40)	3.6

[a–e]See corresponding footnotes in Table 1.

analogues **36** and **37** had improved selectivity over 5-HT_{2A} but reduced oral activity. Incorporation of diazines was moderately successful giving compounds **38–41** with good 5-HT_{2C} affinity and selectivity over 5-HT_{2A}, although unfortunately, none of these achieved 100-fold selectivity over the 5-HT_{2B} receptor. These compounds also had good oral activity in the hypolocomotion model, in particular the pyridazines **38** and **39**.

Summary

A number of bisaryl ethers have been identified with excellent 5-HT_{2C} affinity and selectivity over both the 5-HT_{2A} and 5-HT_{2B} receptors in addition to a range of other monoamine receptors, including serotinergic and dopaminergic subtypes. In a human 5-HT_{2C} receptor functional assay they were found to be inverse agonists completely abolishing basal activity.[4] A number of compounds from this series such as **11**, **27** and **38** demonstrated potent oral activity in the rat hypolocomotion assay and are being further investigated for their potential as novel non-sedating anxiolytics and antidepressants.

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